# Hypernatremia in the intensive care unit

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**Purpose of review**
Hypernatremia is a relatively frequent electrolyte disorder seen in critically ill patients. As many as 27% of patients in intensive care units (ICUs) develop hypernatremia of variable severity during an ICU stay. Debate among specialists often ensues as to whether to correct hypernatremia or not. Some practitioners, particularly intensivists, believe that correction of hypernatremia with fluids may cause expansion of the extracellular fluid volume (ECFV) thereby worsening ventilation and impeding extubation. Other practitioners, including many nephrologists, do not expect correction of hypernatremia to lead to clinically apparent ECFV expansion, and fear other deleterious effects of hypernatremia. In this review we address the controversy regarding appropriate practice.

**Recent findings**
There are no randomized, clinical trials (RCTs) to guide the administration of electrolyte-free fluid administration in hypernatremic patients. However, there are associations, demonstrated in the literature, suggesting that hypernatremia of any severity will increase the mortality and length of stay in these patients. These associations generally support the practice of correction of hypernatremia. In addition, our knowledge of the distribution of total body water influences us towards correcting hypernatremia as an appropriate therapy. We do not expect that adequate RCTs addressing this question will be performed.

**Summary**
Allowing persistence of any degree of hypernatremia is associated with increased mortality, length of stay (LOS) and postdischarge mortality. We expect that proper use of electrolyte-free water intake will avoid adverse outcomes.

**Keywords**
extracellular fluid, fluid therapies, intensive care unit, pulmonary edema, respiratory distress syndrome, water-electrolyte imbalance

## INTRODUCTION

### Case description

A 94-year-old man with a history of dementia was admitted from a nursing home after being found to be lethargic. A week prior to admission he was reported to have decreased oral intake and was refusing food and water. Examination revealed an ill-appearing, elderly man with a heart rate of 70 beats per minute, respirations of 19 breaths per minute, and blood pressure 120/70 mmHg. Physical exam showed no rales or edema and was unremarkable except for his nonfocal neurologic exam which demonstrated an inability to reply to any questions. Serum laboratory studies demonstrated: sodium concentration 161 mEq/l; chloride 122 mEq/l; potassium 3.4 mEq/l; bicarbonate 23 mEq/l; serum glucose 105 mg/dl; serum urea nitrogen 107 mg/dl; serum creatinine 2.6 mg/dl, hemoglobin 13.7 g/dl; serum albumin 2.7 g/dl; calcium 8.5 mg/dl, B-type natriuretic protein 397 pg/ml. His $O_2$ saturation was 93%. His chest radiograph showed no acute cardiac disease with minimally increased interstitial markings. The nephrology consult recommends intravenous 5% dextrose solution at 100 ml/h. The intensivists are reluctant because of the question about his extracellular fluid volume status and oxygenation.

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## KEY POINTS

- Hypernatremia is associated with adverse outcomes, reduced cardiac output, and increased length of stay.
- Correction of hypernatremia has not been shown to have adverse effects and is not expected to cause pulmonary edema.
- Unlike hyponatremia, the rate of correction of hypernatremia in adults does not seem to be clinically significant, with faster rates not causing seizures or cerebral edema.
- Children may be more susceptible to adverse effects of rapid correction.
- Limited data suggest that mild hypernatremia (145–150 meq/l) may have beneficial effects on outcomes in patients with primary respiratory disease.

## DEVELOPMENT OF HYPERNATREMIA IN CRITICALLY ILL PATIENTS

Hypernatremia is defined as a serum sodium concentration exceeding 145 meq/l. It is a disorder frequently seen in intensive care unit patients. Hypernatremia most often develops because of loss of electrolyte-free water. Less frequently, but especially in hospitalized patients, it may also occur by gain of sodium via infusion of sodium-containing solutions such as isotonic 0.9% normal saline [1]. In a retrospective study, hypernatremia was reported in 9% of patients admitted to a Dutch medical ICU [2]. An additional 6% of patients developed hypernatremia during their ICU stay. Upon admission to the ICU, between 2% and 6% of patients are already hypernatremic [3,4]. As many as 6–26% of patients become hypernatremic during the course of treatment in medical and surgical ICUs [3,5,6].

Hypernatremia is the result of loss of electrolyte-free water or a gain of sodium, or a combination of both [7]. Regardless of the etiology, it is always associated with hyperosmolality. In normal people, plasma osmolality is sensed by the hypothalamus and thirst is stimulated. The experience of thirst drives intake of water and avoidance of hypernatremia. Therefore, the development of hypernatremia always implies an inability of the patient to respond to the increase in plasma osmolality. The patient's thirst mechanism may be impaired because of disease of the central nervous system (CNS) or because of the administration of sedative-hypnotic drugs. In other cases, although experiencing thirst, the patient is unable to access water. Such scenarios occur when patients are in restraints, are intubated, unconscious, or cannot express thirst to staff. Young children cannot express the experience of thirst. In ICU settings, when hypernatremia develops as the result of the administration of sodium-containing fluids intended to correct reduced effective arterial blood volume, patients may not be able to communicate thirst to the nursing staff and do not have access to water [7,8].

Efforts to correct perceived hypovolemia, as in the case presented above, are often associated with the administration of large amounts of fluids which are often hypertonic compared with the ongoing fluid losses. Administration of potassium, the dominant intracellular osmole, for correction of hypokalemia, can also trigger the development of hypernatremia. In addition, the administration of loop diuretics leading to loss of hypotonic urine can cause a rise in serum sodium levels [1].

Studies have found hypernatremia to be an independent predictor for mortality and length of stay after controlling for illness severity and other ICU-acquired conditions and complications. Hypernatremia was associated with a 40% increase in risk for hospital mortality and a 28% increase in ICU length of stay. Even a mild degree of hypernatremia, from 145 to 149 mEq/l, was associated with a 28% increase in risk for mortality and a 19% increase in ICU length of stay [9].

## DELETERIOUS EFFECTS OF HYPERNATREMIA

Conclusive evidence of deleterious effects of hypernatremia on human physiology are sparse. Some studies have shown adverse effects of hypernatremia on cardiac physiology. In a study of dogs, increasing serum sodium level and osmolality had negative chronotropic effects [10]. In addition, sodium concentration and osmolality had independent effects on myocardial contractility. Hyperosmolality and hypernatremia caused negative inotropic responses whereas hyponatremia caused a positive one.

Electrocardiographic (ECG) changes are frequently observed. Hypernatremia has been shown to cause low voltage, QT prolongation, and T-wave flattening. Cases of T-wave inversion, mimicking ischemia, have been described. A limited number of case reports of extreme hypernatremia have demonstrated a variety of electrocardiographic abnormalities. However, these reports are confounded by intracranial pathology, cerebral hypertension and severity of plasma sodium concentration. An exception to these anecdotes is a prospective study of subarachnoid hemorrhage in which the primary predictor of outcomes was the serum sodium concentration [11]. Among 214 subjects, 22% were hypernatremic (>143 meq/l on at least one study day), and 21% were hyponatremic (less than



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133 meq/l). After multivariate adjustment, hypernatremia was an independent predictor of left ventricular ejection fraction less than 50% (odds ratio [OR] 4.7, confidence interval [CI] 1.3–16.2, $P = 0.015$), elevated troponin levels (OR 3.7, CI 1.2–11.9, $P = 0.028$), and pulmonary edema (OR 4.1 CI 1.4–1.5, $P = 0.008$); however, it was not a statistically significant predictor of mortality ($P = 0.075$).

The pathophysiologic mechanism by which hypernatremia causes cardiac dysfunction is unknown. One hypothesis is that increased extracellular sodium concentration causes more calcium to exit the cell via the sodium-calcium exchanger at the sarcolemma membrane. This effect results in reduced levels of intracellular calcium levels available for cardiac myocyte contraction, causing a negative inotropic effect. These effects on ion flux may also contribute to hypernatremia being arrhythmogenic [12].

A benefit of correction of hypernatremia, suggesting its adverse influences, was shown in a study of five patients whose mean sodium level was $173 \pm 1.3$ mEq/l and serum osmolality $392 \pm 12$ mosm/kg as the result of receiving sodium bicarbonate during cardiac resuscitation [13]. Patients were treated with 5% fructose intravenously until serum sodium concentration was 150 meq/l. Cardiac index improved in all patients (mean $1.9 \pm 1.7$ l/min-m$^2$ pretherapy and $3.1 \pm 1.01$/min-m$^2$ posttherapy). Pulmonary capillary wedge pressure increased in patients with normal ventricular function and decreased in patients with preexisting congestive heart failure. The authors concluded that the hyperosmolar state decreased myocardial function. These case reports are difficult to interpret given the multiple pathophysiologies underlying the patients' presentations. None experience hypernatremia as an isolated variable, independent of other relevant potential co-morbidities.

Hypernatremia has also been associated with increased mortality after hospital discharge. In a single center study of 59 901 patients who were discharged with hypernatremia, increased one year mortality of 49.4% was observed in patients with serum sodium level of 143–147 meq/l as compared to 17.2% in patients with serum sodium level of 138–142 meq/l. Hospital discharge serum sodium values of 148 mEq/l or higher were significantly associated with nearly fourfold increased odds of 1-year mortality compared with values of 138 to 142 mEq/l [14▪▪]. Whether the serum sodium concentration itself is a cause of these negative outcomes or simply a marker of underlying pathology is not clear. When adjustment was made for potential confounders, one-year mortality was significantly higher in patients who were discharged with serum sodium less than or equal to 137 and greater than or equal to 143 mEq/l, compared with discharge serum sodium of 138–142 mEq/l. The patients with the highest mortality risk were those with discharge serum sodium concentrations of more than 148 mEq/l (hazard ratio [HR] 3.86; 95% CI 3.05–4.88), significantly greater than the risk associated with discharge serum sodium concentrations of less than 132 mEq/l (HR 1.43; 95% CI 1.30–1.57). Whether more aggressive normalization of serum sodium concentration would affect these outcomes is not known. There are several possible mechanisms that have been implicated for the impaired long-term survival in this group. As discussed above, increased serum sodium concentration has been associated with decreased left ventricular contractility; perhaps this effect would fail to correct if serum sodium was not corrected [10]. Increased peripheral insulin resistance and neuromuscular disturbances, including gait abnormalities, are also observed and might contribute to adverse outcomes [13,15,16▪▪].

A primary organ affected by hypernatremia is the brain. Hyperosmolality moves water from the intracellular space and causes loss of cell volume. Brain shrinkage induced by hypernatremia can cause vascular rupture, with cerebral bleeding, subarachnoid hemorrhage, and permanent neurologic damage or death. More frequently, chronic hypernatremia may be suspected of causing defects in cognitive function, gait and balance. The loss of cerebral volume is countered by a prompt adaptive response which consists of solute gain by the brain, which tends to restore lost water. This response can lead to the normalization of brain volume and account for the relatively milder symptoms of hypernatremia that develop slowly [17,18]. However, the normalization of brain volume does not correct hyperosmolality in the brain. In patients with prolonged hyperosmolality, rapid or aggressive treatment with hypotonic fluids may cause cerebral edema, which can lead to coma, convulsions, and death [19–21].

## POTENTIAL BENEFIT OF HYPERNATREMIA WITH LUNG INJURY

There is a theoretical basis for considering that hypertonicity has favorable effects on a variety of pulmonary effects, almost exclusively observed in studies of animal models. In an animal model of hemorrhagic shock, resuscitation with hypertonic saline significantly reduced albumin leak, bronchoalveolar lavage fluid neutrophil counts, and the degree of histopathologic injury compared with resuscitation with Ringer's lactate. Both in vivo and in vitro data suggest that this beneficial effect may be related to altered adhesion molecule expression

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by neutrophils [22]. Similarly, resuscitation after hemorrhagic shock in mice attenuates early polymorphonuclear cell adhesion and pulmonary accumulation, possibly attenuating white cell-mediated organ damage [23]. In addition, hyperosmolality selectively inhibited endothelial-dependent components of the inflammatory response and host defense mechanisms [24].

These effects are invoked as possible explanations for the lack of adverse outcomes observed in respiratory patients with hypernatremia. A study of serum sodium concentration at admission to an ICU from the Australian and New Zealand Intensive Care Society Adult Patient Database included 436 209 eligible patients [25▪]. Mortality risk was referenced in comparison to the group with serum sodium of 135–144.9 meq/l. The mortality risk was U-shaped at the extreme levels of sodium concentration: the adjusted odds ratio (with 95% confidence intervals) for ICU mortality for highest serum sodium (≥160 meq/l) and lowest serum sodium (115–120 meq/l) were 4.2 (3.6–4.9) and 1.6 (1.4–1.8), respectively. However, while this relationship held for various sub-groups, it did not hold for patients with primary respiratory diagnoses ($n = 52\,043$) where the odds ratio for ICU mortality was not significantly influenced by a high serum sodium (1.3 [0.7–1.2]). On the other hand, hypernatremia retained its adverse effect on mortality among patients with primary respiratory diagnoses, whether mechanically ventilated or not, admitted with arterial pressure of oxygen ($PaO_2$)/fraction of inspired oxygen ($FiO_2$) ratios of greater than 200 mmHg; patients with more severely impaired oxygenation ($PaO_2$)/($FiO_2$ less than 200 mmHg) were not adversely affected.

Based on these observations, a randomized trial in moderate-to-severe acute respiratory distress syndrome (ARDS) compared standard care with intravenous hypertonic saline [26▪▪]. The goal of the hypertonic saline intervention was to achieve and maintain plasma sodium between 145 and 150 meq/l for 7 days. The primary outcome was 1-point reduction in lung injury score (LIS) or successful extubation by day 7. Among the patients treated with hypertonic saline, 75% (15/20) of patients were extubated or had ≥1-point reduction in LIS compared with 35% (7/20) in the control group ($P = 0.02$). The length of mechanical ventilation and hospital length of stay were lower in the hypertonic saline group.

## MANAGEMENT OF HYPERNATREMIA

It is evident that hypernatremia of any severity is associated with adverse outcomes. One would then imagine that correcting brain volume and cardiac contractility would not be controversial. Some authors have instead promoted the practice of not completely correcting hypernatremia in critically ill patients. The rationale for this notion is that treating hypernatremia will increase intravascular volume and left ventricular end-diastolic pressure, thereby causing pulmonary edema.

This concern regarding impending extracellular fluid volume overload resulting from correction of hypernatremia can be addressed with concepts of fluid dynamics. Electrolyte-free water moves across compartments in response to osmolality (where membranes express the requisite aquaporins) [27]. The amount of water which fills the intracellular, interstitial and intravascular compartments is in proportion to the size of the compartment. Administration of electrolyte-free water to patients with hypernatremia proportionately supplements the intracellular volume, which represents about two thirds of total body water, rather than the extracellular fluid volume. The extracellular fluid volume is comprised of the intravascular and interstitial compartments, which represent the other third. Of that extracellular compartment, about three quarters is interstitial and one quarter is intravascular. Therefore if 1 l of electrolyte-free water was to be administered to a hypernatremic patient, the volume expected to remain in the vascular space, potentially contributing to the cardiac preload would be one quarter of 333 ml, or only 83 ml. The contribution of this small volume to left ventricular end-diastolic pressure and alveolar fluid content will not be clinically significant and could be countered by administration of diuretics. While the latter may cause loss of hypotonic urine that may increase serum sodium concentration, it will simply necessitate more electrolyte-free water administration [28].

Management of hypernatremia should be directed towards treating underlying causes such as gastrointestinal volume loss, pyrexia, and hyperglycemia. Cathartics and lithium should be discontinued if possible. Diuretics may be appropriate if augmentation of sodium losses is appropriate. Diluting enteral or parenteral feeds by adding electrolyte-free water while maintaining desired doses of calories may be helpful. In patients with hypernatremia that has developed over a period of hours (e.g., those with accidental sodium loading), rapid correction improves the prognosis without increasing the risk of cerebral edema, because accumulated electrolytes or solutes are rapidly extruded from brain cells [17,29]. In such patients, reducing the serum sodium concentration by 1 mEq/l per hour is appropriate. The rate of correction, however, may not be critically important, unlike the case in hyponatremia, as demonstrated in a recent review of patients who had severe hypernatremia on admission and in those who developed hospital-acquired



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hypernatremia [30▪▪]. There was no significant difference in in-hospital 30-day mortality rates between rapid (>0.5 meq/l per hour) and slower (≤0.5 meq/l per hour) correction rates. No cases of cerebral edema attributable to rapid hypernatremia correction were identified. Children with hypernatremia may be more sensitive to rates of correction of serum sodium [28].

The possibility that treating hypernatremia may be adverse for pulmonary outcomes in patients with ARDS is raised by the recent randomized controlled trial cited above [26▪▪]. We would suggest that treating patients with serum sodium values higher than those targeted in that trial, 145–150 meq/l, would be appropriate until additional studies of a greater range of values become available.

The preferred route for administering fluids is the oral route or a feeding tube; if neither is feasible, fluids should be given intravenously. Only hypotonic fluids are appropriate, namely 5% dextrose, which is 100% electrolyte-free water (dextrose is present only to prevent lysis of red blood cells and is irrelevant to changes in sodium concentration assuming the action of insulin). The more hypotonic the infusate, the lower the infusion rate required. Except in cases of frank circulatory compromise evident on admission when the history is consistent with loss of extracellular fluid volume, 0.9% sodium chloride (isotonic, or normal saline) is unsuitable for managing hypernatremia [15,31,32].

Infusing 5% dextrose may be challenging in patients with hyperglycemia because hyperglycemia itself leads to poor outcomes in critically ill patients. An increase in insulin dosing may be required. Other hypotonic solutions like 0.225% saline (1/4 normal saline) without dextrose have been studied in patients with hyperglycemia when gastric tube infusion is not tolerated. It is relatively safe and efficacious but leads to minor degrees of hemolysis as judged by increases in free plasma hemoglobin [33]. Despite that finding, acute kidney injury was not noted. If utilized, 0.225% saline should be given through a central venous catheter which is believed to cause rapid distribution of fluid and thereby decrease the magnitude of hemolysis. Similarly, sterile water without dextrose has been used in similar situations [34,35].

## CONCLUSIONS

Most clinical observations demonstrate that hypernatremia is associated with adverse outcomes, including reduced cardiac function and increased length of hospital stay. Although randomized controlled trials regarding protocols for management of hypernatremia are lacking, guidelines for managing hyponatremia are based on a more robust set of observational series and animal models [28]. Correction of hypernatremia has not been shown to have adverse effects. Observational data show that hypernatremia may not portend increased mortality in patients with a primary respiratory diagnosis, and there is now limited evidence of a potential benefit of induced hyperosmolality in ARDS. In such patients, tolerating a mild degree of hypernatremia may now be appropriate.

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### Conflicts of interest

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